# ClinOleic

**Name of the Drug**: ClinOleic 20%

**Composition:**
Sterile fat emulsion containing a mixture of refined olive oil (approximately 80%) and refined soya oil (approximately 20%) 200 g, egg lecithin (purified egg phospholipids) 12 g, glycerol 22.5 g, sodium oleate 0.3 g and Water for Injections to 1,000 mL (final pH between 6.0-8.0).
One of the active ingredients, soya oil, contains ascorbyl palmitate as an antioxidant, (free radical scavenger), in the concentration of 0.15 mg per gram of oil.

**Description:**
ClinOleic 20% is a milk-like homogeneous liquid. ClinOleic 20% is an isotonic emulsion. It has an osmolality of approximately 345 mOsmL/kg water and energy content of 8360 kJ (2,000 kcal) per 1000 mL. The relative density of ClinOleic 20% is in the range of 0.983 – 0.989.

**Pharmacology:**
Pharmacological actions -
ClinOleic 20% provides a moderate proportion of essential fatty acids (EFA), which probably facilitates their utilisation. The combination of olive and soya oils allows a content of fatty acids in an approximate ratio of:

- Saturated fatty acids: 15% (SFA)
- Mono-unsaturated fatty acids: 65% (MUFA)
- Essential Poly-unsaturated fatty acids: 20% (EPUFA)

For patients requiring complete parenteral nutrition, complementary carbohydrates, amino acids, electrolytes, vitamins, and trace elements supplements are required.

ClinOleic 20% is a source of energy; the high-energy content of the emulsion enables the administration of a large quantity of calories in a small volume.
ClinOleic 20% also contains glycerol for isotonicity.
Egg lecithin supplies phosphorus and choline.

Pharmacokinetic properties -
In ClinOleic 20%, most of the lipid particle sizes are in the range of chylomicrons (0.08 – 0.6 micrometers) with the mean diameter of less than 0.45 micrometers.
However, it may contain a small fraction (up to 2.5 %) of particles having a diameter of more than 1 micrometer.

**Clinical Trials**
ClinOleic has been used in a number of small clinical trials generally using Intralipid as a comparative agent. The numbers enrolled in these trials were small and they are not suitable for data pooling or meta-analysis or for demonstrating non-inferiority to the comparator. The studies were of variable duration. The studies usually measured fatty acid composition of plasma lipid fractions. 32% of the adult patients studied were aged over 65 years old.

The two (2) pivotal studies enrolled 59 infants and children aged under eleven (11) years old.

- Study CT 2402/P14/93/F ("Ricour Study"), double-blind, randomised, parallel group, measured the level of fatty acids in plasma phospholipids (primary efficacy variable) and compared the long-term efficacy and safety of ClinOleic 20% (n=9) to Intralipid 20% (n=9) in children and infants who needed prolonged Parenteral Nutrition (PN) at home or hospital. Seventeen (17) patients aged from 1 to 9 years old were exposed for two (2) months and one (1) patient was exposed for one (1) month.

  The results of the study are shown in the following table:

  Table 1: Primary efficacy variable: fatty acids in plasma phospholipids

| | Day 0 | Day 60 |
|---|---|---|
| Oleic acid (C18: n-9) (p=0.0023) | | |
| ClinOleic | 10.7 | 14.5 |
| Intralipid | 9.2 | 9.9 |
| Linoleic acid (C18: 2n-6) (p=0.0001) | | |
| ClinOleic | 16.6 | 13.9 |
| Intralipid | 17.6 | 20.2 |
| C20: 4n-6/C18: 2n-6 (p=0.0001) | | |
| ClinOleic | 0.58 | 0.70 |
| Intralipid | 0.59 | 0.45 |
| n-6 metabolites/C18: 2n-6 (p=0.0001) | | |
| ClinOleic | 0.82 | 0.96 |
| Intralipid | 0.83 | 0.64 |

- Study CT 2402/P15/94/G ("Koletzko Study"), double- blind, randomised, parallel group, compared the efficacy and safety of ClinOleic 20% (n=22) to Intralipid 20% (n=20) in premature infants requiring lipid based TPN for 7 days. Forty-two (42) premature infants aged -gestational age- 28 to 36 weeks ± 6 days were exposed.

  The results are shown in the following table:

  Table 2: Primary efficacy variable: n-6 and n-3 metabolites fatty acids; mead acid; arachidonic acid.

| | Day 0 | Day 8 |
|---|---|---|
| n-6 metabolites (p=0.19) | | |
| ClinOleic | 16.8 | 13.3 |
| Intralipid | 17.7 | 13.0 |
| n-3 metabolites (p=0.73) | | |
| ClinOleic | 3.39 | 2.73 |
| Intralipid | 3.68 | 3.09 |
| Mead acid (C20: 3n-9) (p=0.03) | | |
| ClinOleic | 1.15 | 1.04 |
| Intralipid | 0.72 | 0.20 |
| Arachidonic acid (C20: 4n-6) (p=1.0) | | |
| ClinOleic | 13.3 | 9.2 |
| Intralipid | 14.1 | 9.5 |

Tolerability of the emulsions in the treatment and control groups was similar.

**Indications:**
Parenteral nutrition when oral or enteral nutrition is impossible, insufficient or contra-indicated.

**Contraindications:**
- Hypersensitivity to the active substance or to any of the excipients (e.g.: egg or soybean protein)
- Severe dyslipidaemia and non corrected metabolism disorders including lactic acidosis and uncompensated diabetes,
- Severe sepsis,
- Severe liver disease,
- Blood coagulation disorders, thrombophlebitis,
- Acute and chronic renal failure, in absence of specific studies, there is insufficient data to justify its use in acute/chronic renal failure
- Myocardial infarction

**Precautions:**
Special clinical monitoring is required at the beginning of any intravenous infusion. Should any abnormalities occur, the infusion must be stopped.

Use with caution in the following circumstances -
Any signs of anaphylactic reaction (as for example fever, shivering, skin rash, dyspnoea, etc.) should be cause for immediate discontinuation of the infusion.

Extremely premature and/or very low birth-weight infants receiving ClinOleic 20% should be under the close supervision of a neonatologist. Clinical experience exists for administration of ClinOleic 20% for up to 7 days in neonates and up to 2 months in children.

ClinOleic 20% should be administered with caution in the case of neonatal hyperbilirubinemia (total serum bilirubin > 200 μmol/l). Total bilirubin levels should be monitored closely.

The use of ClinOleic in patients with chronic liver disease without systemic failure has not been evaluated. The condition as well as the function of the liver should be closely followed if ClinOleic is to be used in these patients.

Fat metabolism may be disturbed in uncompensated diabetes. The use of ClinOleic in patients with diabetes mellitus has not been investigated. If ClinOleic is administered the elimination of fat should be monitored daily.

*Check the following before use -*
Plasma triglyceride levels and clearance should be monitored daily. The triglyceride concentration in serum during infusion should not exceed 3 mmol/l. Infusion should only be started when serum triglyceride levels have returned to baseline level.

During short-term or long-term intravenous nutrition, alkaline phosphatase and total bilirubin should be checked at regular intervals, depending on the health status of the patient.

Fluid balance, electrolytic or metabolic disorders should be corrected before administration of ClinOleic 20%.

Fat emulsions should be administered simultaneously with carbohydrates and amino acids to avoid metabolic acidosis.

Blood sugar, acid-base balance, electrolytes, water balance and blood counts must be checked at regular intervals.

Carcinogenicity, mutagenicity and impairment of fertility -
Tests for carcinogenicity, mutagenicity and effects on fertility have not been conducted with Clinoleic 20%.

Use in pregnancy (Category – exempt)
The safety of administration of ClinOleic 20% during pregnancy has not been established. No reproductive toxicity studies with ClinOleic 20% have been carried out in animals, and its use in pregnancy is not recommended.

*Use in lactation -*
The safety of administration of ClinOleic 20% during lactation has not been established. Therefore, ClinOleic 20% should be used during lactation only if clearly needed.

*Interactions with other drugs -*
Complete information about incompatibilities is not available.

- Electrolytes or medication should not be added directly to the lipid emulsion.
- If it is necessary to introduce additives to a solution containing ClinOleic 20%, first verify the compatibility and then mix thoroughly before administration to the patient.
- The compatibility of drugs intended for administration by the Y-site of an infusion containing ClinOleic 20%, must first be established

*Compatibility with other drugs and nutrients -*
ClinOleic 20% may be included as a component of parenteral nutrition admixtures incorporating carbohydrates and amino acids where compatibility and stability have been established. Admixing should be accompanied by gentle agitation during preparation under strict aseptic conditions.
The addition of polyvalent electrolytes to an admixture requires thorough review of the interaction of calcium and phosphate. This review should be made before compounding is initiated, due to the possible interaction between the calcium and the phosphate.
In the case of Synthamin amino acid solutions with electrolytes, the limits of these electrolytes should be less than or equal to 5.0 mmol/L for calcium, and phosphates should not exceed a concentration of 30 mmol/L from all sources.
Absolute solubility of calcium/phosphate in parenteral admixtures is dependent upon many factors, including the concentration of amino acids in the admixture. Reference should be made to calcium/phosphate solubility curves; (appropriate to the amino acid in use), published by the amino acid solution manufacturers, to determine the solubility limits before admixing commences.
"Breaking" or "oiling out" of the emulsion can be visibly identified by accumulation of yellowish droplets or particles in the admixture.

*Compatibility with containers and administration sets -*
Phthalate plasticisers are extracted from PVC bags and administration sets by intravenous fat emulsions. PVC bags and administration sets should not be used for delivery of ClinOleic 20% or of solutions containing ClinOleic 20%. Bags made from ethyl vinyl acetate (EVA) and administration sets made from non-plasticised materials are recommended.

*Effects on laboratory tests* -
As with all lipid emulsions, ClinOleic 20% may interfere with certain laboratory measurements (bilirubin, haemoglobin, lactate dehydrogenase, oxysaturation), if blood is sampled before fat has adequately been cleared from the bloodstream. In most patients, fat is cleared after a fat free period or interval of 5 to 6 hours.

**Adverse reactions:**
During administration of parenteral nutrition fat emulsions, two types of adverse reactions can occur:

- *Immediate reactions*:
  At the beginning of the infusion, any of the following abnormal signs evoking a hypersensitivity reaction should be cause for immediate discontinuation of the infusion: sweating, shivering, cephalgia, dyspnoea.

- *Delayed reactions*:
  During long-term parenteral nutrition of fat emulsions, the following adverse reactions have been observed:

  Hepato-biliary disorders:
  - increase of alkaline phosphatase, bilirubin and transaminases (ALT & AST)
  - hepatomegaly
  - icterus

  Blood and lymphatic System disorders:
  - thrombocytopenia

Of the clinical trials performed with ClinOleic 20%, a summary of the serious adverse events (SAE) are summarised in Table 3. Over a period from November 1995 to November 2003, sixteen (16) SAE's were reported in clinical studies. Of the 16 AE's, seven (7) were not related, one (1) possibly related and one (1) unlikely related to the product administration. The total number of units used during this period was 1,325,117.
To date, two (2) spontaneous adverse events were reported.

Table 3: Adverse Reactions report by System Organ Class classification. Post-marketing experience, PSUR 1995-2003.

| System Organ Classification | Sources | |
|---|---|---|
| | **Clinical Trials** | **Spontaneous** |
| **Serious adverse events** | | |
| 1. Body as a whole | 8 (8/16=50%) | |
| • Fever | 1 N/R | |
| • Septicemia | 3 N/R | |
| • Sepsis | 4 N/R | |
| • Allergic reaction | | 1 P/R |
| 2. Central Nervous System | 3 (3/16=19%) | 0 |
| • Cerebral edema | 1 N/R | |
| • Convulsion | 1 N/R | |

| | | |
|---|---|---|
| 3. Respiratory system<br>• Pneumonia (fatal)<br>• Respiratory insufficiency | 2 (2/16=16%)<br>1 P/R<br>1 U/R | 0 |
| 4. Cardiovascular system<br>• Arrhythmia<br>• Increased blood level of immunosuppressant drug | 2 (2/16=16%)<br>1 N/R | <br><br>1 N/R |
| 5. Musculo-skeletal system<br>• Bone necrosis | 1 (1/16=6%)<br>1 N/R | 0 |
| TOTAL | 16 | 0 |

N/R – Not Related
P/R – Possibly Related
U/R – Unlikely Related

**Dosage and administration:**

*Dosage -*

*Note*: the percentage (%) of lipid in the ClinOleic 20% formulation is expressed in weight by volume (w/v). That is, 5 mL of ClinOleic 20% contains 1 gram of lipid.

- *Adult*:
  The dosage is 1 to a maximum of 2 g lipids/kg/day.

  Never exceed 0.15 g lipids/kg/hour (0.75 mL/kg/hour).

| | Adults per kg of body weight | 70 kg adult |
|---|---|---|
| Usual lipid dosage | 1 to 2 g/kg/day | 70 to 140 g/day |
| Infused volume of ClinOleic 20% | 5 to 10 mL/kg/day | 350 to 700 mL/day |

- Children:
  It is recommended not to exceed a daily dose of 3g lipids/kg of body weight and an infusion rate of 0.15 g lipids/kg of body weight/hour.
  Daily dose should be increased gradually during the first week of administration.

- Premature newborns and low birth weight infants:
  The use of ClinOleic 20% is restricted to premature infants of 28 weeks gestational age or more.
  The initial daily dose should be 0.5-1.0g lipids/kg of body weight. The dose may be increased by 0.5-1.0g lipids/kg of body weight every 24 hours up to a daily dose of 2.0 g lipids/kg of body weight.

*Flow rate and duration -*

- *Adult:*
  The initial infusion rate must be slow and not exceed 0.1 g lipids or 0.5 mL (10 drops) per minute for 10 minutes then gradually increased until reaching the required rate after half an hour.

- Children:

ClinOleic 20% should be administered as a continuous 24h/day infusion.
It is recommended not to exceed an infusion rate of 0.15 g lipids/kg of body weight/hour.
Daily dose should be increased gradually during the first week of administration.

- Premature newborns and low birth weight infants:
  ClinOleic 20% should be administered as a continuous 24h/day infusion.

*Route of administration -*
Intravenous infusion:

- when administered as part of a complete nutrition admixture (with glucose and amino acids) the central or peripheral venous route should be chosen depending on the osmolarity of the final admixture.
- in rare cases, when infused alone as a complementary support to oral or enteral nutrition, ClinOleic 20% can be administered via peripheral vein.

ClinOleic 20% infusion does not contain an antimicrobial agent. To avoid the risk of microbial contamination, infusion should be commenced as soon as practicable after the preparation of an admixture. As with all parenteral administration, particularly infusions, strict aseptic technique should be used at all times. ClinOleic 20% intravenous infusion is for single use only in a single patient.

*Method of preparation-*
The order of mixing is critical to ensure compatibility and stability of admixtures containing ClinOleic 20%. Use aseptic technique all way through the compounding processes. Thorough mixing after the addition of each component is essential. ClinOleic 20 % and other components of Parenteral Nutrition do not contain anti-microbial agents. Therefore, once mixed, the admixtures should be administered over a period not exceeding 24 hours.
ClinOleic 20% may be combined with other nutrients by adding the emulsion to a mixture of amino acids and glucose in fixed proportions.

Thus for example, an extemporaneous formulation made of amino acid, Synthamin® 9, with electrolytes (500mL), Glucose solution 10% (375mL) and ClinOleic 20% (250mL) could be prepared without the risk of instability. Some combinations of 3-in-1 TPN admixtures are shown in Table 4.

Table 4:
Recommended 3-in-1 TPN admixtures
(Synthamin ® (w/e), Glucose and ClinOleic 20%)

| **Amino Acid (mL) *** | **Glucose (mL)** | **ClinOleic 20% (mL)** | **Total Vol (mL)** |
|---|---|---|---|
| Synthamin® 9 (500) | Glucose 10% (375) | ClinOleic 20% (250) | 1125 |
| Synthamin® 9 (500)<br>Synthamin® 17 (500) | Glucose 10% (125)<br>Glucose 20% (125) | ClinOleic 20% (250) | 1500 |
| Synthamin® 9 (250) | Glucose 10% (188) | ClinOleic 20% (250) | 688 |
| Synthamin® 17 (400) | Glucose 20% (95) | ClinOleic 20% (250) | 745 |

| | | | |
|---|---|---|---|
| Synthamin® 9 (425) | Glucose 30% (400)<br>Glucose 50% (200) | ClinOleic 20% (200) | 1225 |
| Synthamin® 17 (625) | Glucose 50% (425) | ClinOleic 20% (200) | 1250 |
| Synthamin® 9 (250) | Glucose 50% (250) | ClinOleic 20% (250) | 750 |
| Synthamin® 17 (375) | Glucose 70% (150) | ClinOleic 20% (250) | 775 |
| Synthamin® 9 (250)<br>Synthamin® 13 (250) | Glucose 30% (125)<br>Glucose 50% (125) | ClinOleic 20% (250) | 1000 |

* All amino acid solutions contain electrolytes
[Note: w/e=with electrolytes]

The registration numbers for the amino acids are, Synthamin® 9 w/e (AUST R19451), Synthamin® 13 w/e (AUST R 19447) and Synthamin® 17 w/e (AUST R 19449).
The order of admixing of the above components should be approached by minimising a sudden change in the negative charge of the emulsion. Firstly, mix the glucose infusion with the amino acid infusion. ClinOleic 20% emulsion can then be added into this admixture. Finally the electrolyte complements then trace elements can be added.

As the lipid emulsion is negatively charged, do not add electrolytes or trace elements directly into ClinOleic 20% emulsion as they destabilise the emulsion. The recommended sequence for adding electrolytes is monovalent, divalent, and trivalent ions. Phosphates salts must always be added prior to calcium salts as discussed below.

The inclusion of calcium and phosphate ions in a TPN admixture requires special attention to a possible formation of calcium phosphate precipitate, which is affected by pH, temperature, calcium salt, sequence of calcium and phosphate addition to the admixtures and concentration of calcium and phosphates ions. The limits of these electrolytes should be less than or equal to 5.0 mmol/L for calcium and phosphates should not exceed a concentration of 30 mmol/L from all sources. At pH 7.0 and above the addition of $NaH_2PO_4$ to Calcium gluconate solution results in a precipitation of $CaHPO_4$, that is, the equilibrium between $[H_2PO_4]^{-1}$ and $[HPO_4]^{-2}$ is shifted to the $[HPO_4]^{-2}$ side. At pH of 4.1, phosphate ions are predominantly in the form of monobasic phosphate, whilst at a higher pH, it occurs in a form of dibasic phosphate ions. Taking into consideration that the glucose infusion has a pH in the range 3.2 – 6.5, and in order to minimise a formation of dibasic phosphate ions, the sodium monobasic phosphate should be added to the glucose infusion in the early stage of the compounding of a TPN admixture. Then, this admixture is added to the amino acid infusion, which has a buffer capacity and no charge effects at pH 5 – 6. This is followed by the addition of the lipid emulsion to the obtained admixture. Finally, calcium gluconate is added at the end of the TPN compounding process.

Separation of the product (gravity dispersion or “creaming”) may occur after the emulsion has been stored a period of time without agitation. It should only be necessary to invert the bottle or shake the bag 2 or 3 times before use. The product must not be used if the emulsion has a yellow appearance, or is seen to contain yellow droplets of oil. Do not use if shaking does not result in a uniform emulsion.

*Preparation for administration*-

- Bottle:
  Before use check that the emulsion is homogeneous, and that the bottle is free of cracks or splinters.
  All opened bottles must be used immediately and not be stored for further use.
  For single use only. Discard partly used bottle.

- Bag:
  **PLEASE NOTE**
  As lipid emulsions are oxygen sensitive, an oxygen absorber and oxygen indicator are added between the inner bag and the over wrap. The oxygen indicator shows whether oxygen has entered the packaging due to damage of the overwrap. The oxygen indicator should be inspected **before** removing the overwrap. If oxygen enters the overwrap and is not absorbed by the oxygen absorber, the oxygen indicator changes colour.
  The oxygen indicator mixture may appear biphasic, as it is a suspension of a solid in a liquid. Once it is determined that the product is safe to use, the sachet should be discarded.

  a. To open:
     - tear the protective over wrap.
     - confirm the integrity of the bag.
     - use only if the bag is not damaged.
  b. Positioning the infusion:
     - suspend the bag
     - remove the plastic protector from the administration outlet.
     - firmly insert the infusion spike into the administration outlet.
  c. Additions:
     If it is necessary to introduce additives, verify the compatibility and mix thoroughly before administration to the patient. Additions must be performed under aseptic conditions. These additions are made into the injection site using a needle:
     - prepare the injection site,
     - puncture the injection site and inject,
     - mix the contents of the bag and the additives (see Method of Preparation*)*.
     - Administration

For single use only.
Do not store partially used bags and destroy all accessory parts after use.
Do not re-connect partially used bags.

**Over dosage:**
In case of overdose (an abnormal rise in triglyceride levels during infusion of fat) where any of the following reactions occur: general symptoms such as fever or evocating an haemodynamic instability, emesis, algia, liver function abnormalities, hepato or splenomegalia, haemostasis disorders, hyperlipidemia, hypersensitivity, fat infusion should be stopped or if necessary, continued at a reduced dosage.

**Presentation:**
*Container* -
ClinOleic 20 % can be packaged:

a. in glass bottle (type II),
b. or in bag container. This bag is a multi-layer plastic bag
(EP-SEBS/EVA/EVA2/PCCE) packaged in an oxygen barrier over wrap.

The product is available in the following sizes:
**In bottle:**
100 mL in bottle - Package sizes: 24 or 10 units.
125 mL in bottle - Package sizes: 10 or 24 units.
250 mL in bottle - Package sizes: 10 or 12 units.
500 mL in bottle - Package sizes: 10 or 12 units.
1000 mL in bottle - Package size: 6 units.

**In bag:**
100 mL in bag: Box of 10 or 24 units.
250 mL in bag: Box of 10 or 20 units.
350 mL in bag: Box of 10 or 12 units.
500 mL in bag: Box of 10 or 12 units.
1000 mL in bag: Box of 6 units.

Not all pack sizes may be marketed.

*Shelf life -*
18 months in glass bottle or in plastic bag in the over wrap.

*Storage condition -*
Store below 25°C
Do not freeze
Protect from light.

**Poison Schedule**: Not scheduled.

**Name and address of the sponsor:**
ClinOleic 20% sterile injectable emulsion is made by Clintec Parenteral, France or Baxter S.A., Belgium and supplied in Australia by
Baxter Healthcare Pty Ltd
1 Baxter Drive, Old Toongabbie, NSW 2146.

ClinOleic 20% bottle AUST R 97538
ClinOleic 20% bag AUST R 97537

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